PROTOCOL

Short Title: OPT (Oxford Postnatal Treatment) Study.

Full Title: Treatment for mothers with postnatal depression to improve child outcome: a randomised controlled trial.

Ethics Ref: 10/H0505/55

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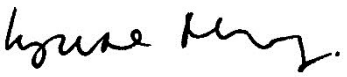

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1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
2	4	7/06/2011	ER & AS	
3	5	20/07/2011	ER & AS	
4	6.0	15/08/2011	VW & AS	
5 Revised	7.0	22/08/2012	VW & AS	Assessment 3 attention additions
6	8.0	19/11/2012	VW & AS	Emotional discrimination task
7	9.0	08/07/2013	EN&AS	Recruitment via websites
8	10.0	17/12/2013	EN & AS	Qualitative project on participants experience of therapy
9	11.0	29/04/2014	EN & AS	Addition of Music Questionnaire at A3 assessment
10	12.0	25/06/2014	EN&AS	1. Clarification of use of Bayley III in the Protocol 2. validation study of a subset of Bayley items
11	12		EN & AS	Addition of 4 questions to the Music Questionnaire
Non-substantial amendment	12.1		EN & AS	Section 9.1 – additional information provided on number of participants needed using the Bayley III.

2. SYNOPSIS

Maternal postnatal depression (PND) is a major public health issue: it affects around 13% of mothers and, compared to children of non-depressed mothers, the children of mothers with PND are more likely to have intellectual, behavioural and attachment problems. Treating maternal depression alone does not improve child outcome. An intervention focusing on mother-child interactions is needed to promote these children's development.

We aim to examine whether, in the context of PND, a treatment to enhance mother-child interactions leads to improved child outcome. Furthermore, since treatment can be targeted at critical aspects of functioning, a treatment trial provides an opportunity to examine potential causal factors in determining child outcome. Thus, we will focus treatment on improving three key parenting capacities that are known to be compromised in PND, and examine whether this improves children's outcomes.

Mothers with PND will receive home-based treatment form six months postpartum. They will be randomised to one of two treatments: either Video Feedback Treatment (VFT; index) to improve mother-child interactions or Progressive Muscle Relaxation (PMR; control). Both groups will also receive Cognitive Behaviour Therapy (CBT) for depression as part of the trial treatment package. The two groups will be compared post-treatment (child age one year) and at follow-up (child age two years).

Study Title	OPT (Oxford Postnatal Treatment) Trial. Treatment for mothers with postnatal depression to improve child outcome: a randomised controlled trial.
Internal ref. no.	
Study Design	Randomised controlled trial.
Study Participants	Mothers with persistent postnatal depression at 6 months postpartum
Number of Participants	144
Planned Study Period	5 years
Primary Objective	In the context of postnatal depression, compared to a control treatment (PMR) does the index treatment (VFT) lead to better cognitive, behavioural and attachment outcomes in the children at 24 months (where mothers in both groups receive CBT for their depression)? It is hypothesised that, compared to the control treatment, VFT will lead to better cognitive development, fewer behaviour problems, and a higher rate of secure attachment.
Secondary Objectives	Does video feedback operate by improving the quality of the three key parenting capacities discussed above? We will test the hypotheses that compared to the control treatment a) VFT will lead to greater improvements in the three parenting capacities (maternal attention on the infant and associated contingency; emotional scaffolding; and treating the child as a psychological agent and behavioural sensitivity to attachment cues); b) improvements in these capacities will mediate the effects of treatment on outcome; and c) each parenting capacity will be specifically linked to a particular conceptually related child outcome as follows: • Improved maternal focus of attention on the infant and associated contingency will mediate better cognitive development • Improved emotional scaffolding will mediate better emotional regulation and fewer behaviour problems • Improved ability to treat the child as a psychological agent and behavioural sensitivity to attachment cues will mediate higher rates

	of secure attachment in the children
Primary Endpoint	1. *Child cognitive development* will be measured using the Bayley Scales of Infant Development-Third Edition (BSID-III). We will use the cognitive and language scales as the principal outcome. This is a widely used and validated measure of cognitive functioning at this age and has recently been updated. 2. *Behaviour problems* will be assessed by the Child Behaviour Checklist (CBCL) (2-3 year-old version) which is widely-used and well-validated. The principal outcome will be the externalising scale of the CBCL using maternal report at 2 years of age. 3. *Attachment security* will be measured by the Attachment Q-Sort (AQS), a 90 item q-set designed to measure the security of a child's attachment behaviour during naturalistic observations in the family home. It has been shown to be reliable with good discriminant validity. The items consist of numerous descriptors of behaviour typical of children between the ages of 12 and 48 months and these items are sorted by trained observers on the basis of extensive observations lasting for at least 1.5 hours.
Secondary Endpoints	i) *Emotion-regulation* Two standardised tests of infant temperament will be used to elicit emotion-regulation in the infants, taken from the LAB-TAB battery, the barrier paradigm and the restraint paradigm. Both are designed to examine emotional regulation in the face of potential frustration and anger. The mean of the emotional regulation scores will be used as a composite measure. ii) *Sustained Infant Attention* – will be measured using both manual responses by the child and eye-tracking using a version of the continuous performance test designed for use with 24-month-olds Early Childhood Vigilance Task. iii) *Maternal depression* will be measured at each time point using the EPDS and SCID. Depression at 24 months will be used as a secondary outcome. Although not an outcome variable, the fathers' depressive symptomatology will also be measured using the EPDS at each timepoint. iv) *Behaviour problems* assessed by the externalising scale of Child

	Behaviour Checklist (CBCL) (2-3 year-old version) using father reports at 2 years of age.
Intervention (s)	Cognitive Behaviour Therapy (CBT) Video Feedback Therapy (VFT) Progressive Muscle Relaxation (PMR)

3. ABBREVIATIONS

AQS	Attachment Q-Sort
BSIDII	Bayley Scales of Infant Development II
BSIDIII	Bayley Scales of Infant Development III
CBCL	Caregivers Behaviours CheckList
CI	Chief Investigator
CTRG	Clinical Trials & Research Governance, University of Oxford
CBT	Cognitive Behaviour Therapy
CRB	Criminal Records Bureau
CSR	Clinical Severity Rating
DAS	Dyadic Adjustment Scale
ECBQ	Early Childhood Behavior Questionnaire
ECVT	Early Childhood Vigilance Task
EPDS	Edinburgh Postnatal Depression Scale
GP	General Practitioner
GCP	Good Clinical Practice
IBQ	(Rothbart) Infant Behaviour Questionnaire
IPPS	Infant-Parent Perinatal Service
IRAS	Integrated Research Application System
MDI	Bayley Mental Development Index
NRES	National Research Ethics Service
OBMH	Oxfordshire and Buckinghamshire Mental Healthcare NHS Trust
OCTUMI	Oxford Clinical Trials Unit for Mental Illness
OPT	Oxford Postnatal Treatment
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
PMR	Progressive Muscle Relaxation
PND	Postnatal Depression
PTSD	Post Traumatic Stress Disorder
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SCID	Structured Interview for DSM IV Diagnosis
SOP	Standard Operating Procedure

VFT	Video Feedback Therapy
IPA	Interpretative Phenomenological Analysis

4. BACKGROUND AND RATIONALE

Maternal postnatal depression (PND) is common with a prevalence of around 13% (O'Hara et al 1996). There is a considerable body of evidence that postnatal depression affects a mother's ability to cope with the care of her infant and limits her capacity to engage positively with the infant in social interactions (see reviews by Field 1995; and Murray and Cooper 2003). A range of studies has shown that PND increases the risks for the child in infancy and beyond, with adverse consequences for the child's cognitive and behavioural development, and attachment (Murray and Cooper 2003). As a result, PND is now recognised as a major public health issue.

The effects of postnatal depression on child development

Cognitive development: Postnatal depression has been found to have an adverse influence on general cognitive functioning, both in infancy and through childhood (see reviews by Sohr-Preston and Scaramella 2006 and Murray and Cooper 2003). A number of studies have found that the negative effects are more likely in more disadvantaged populations (Hay and Kumar 1995, Sharp et al 1995, Stein et al 2008, Petersen et al 2001) and some have shown that boys are more at risk (Sharp et al 1995, Milgrom et al 2004). Chronicity of PND has been particularly associated with worse outcomes in several large-scale studies (Sohr-Preson et al 2006, Petterson and Burke-Albers 2001, NICHD Early Child Care Research Network 1999, Brennan et al 2000). In addition to general cognitive ability, specific cognitive skills, notably child attention (Breznitz and Friedman 1988, Hay et al 2001), has been found to be negatively affected by maternal depression. Our own current work, in collaboration with the large-scale Avon Longitudinal Study of Parents and Children (ALSPAC), indicates that PND has an adverse effect on infant attentional persistence, especially if depression becomes chronic.

Behaviour problems: Adverse effects of PND on behavioural problems have been found in early childhood as well as at school age and beyond, as indicated by informants both inside and outside the family (Murray and Cooper 2003). For example, a number of studies using independent teacher reports have found converging evidence of poor behavioural outcomes (Alpern and Lyons-Ruth 1993, Essex et al 2001, Sinclair and Murray 1998, Essex et al 2003). As with cognitive functioning, boys may be more at risk (Sinclair and Murray 1998). While some studies have shown that early postnatal depression has independent effects on later child behaviour problems (Wrate et al 1985, Dawson et al 2003), and others have not (Brennan et al 2000, Philipps and O'Hara 1991), there is consistent evidence for adverse

effects if the depression becomes chronic (Petterson and Burke-Albers 2001, NICHD Early Child Care Research Network 1999, Alpern and Lyons-Ruth 1993, Trapolini et al 2007).

Children of mothers with PND have also been shown to have difficulties with emotional regulation. For example, in our collaboration with ALSPAC, we have shown that, early PND was associated with difficulties in emotional regulation at 24 months with chronicity depression being a strong predictor of adverse outcome.

Social development/attachment: There is consistent evidence for a relationship between postnatal depression and attachment insecurity (see meta-analyses by Atkinson et al 2000 and Martins and Gaffan 2000). This is, again, particularly likely where the depression is chronic, as evident in a large NICHD study (Campbell et al 2004). Depression in the early postpartum months can also pose a risk to longer-term social development of the child in terms of their social relationships and self competence (Murray et al 2001, Hipwell et al 2005), and again this is particularly evident when mothers remain chronically depressed (Maughan et al 2007, Ashman et al 2008).

Follow-up to adolescence: A few studies have followed up children whose mothers were postnatally depressed into the teenage years, and all have found increased rates of psychiatric disorder (Hammen and brennan 2003, Halligan et al 2007 and Paylby et al 2008).

Critical questions

Two critical questions arise. First, given that treating the mother's depression alone does not lead to improvements in child outcome (Forman et al 2007 and Nylen et al 2006), how do we best treat maternal postnatal depression and promote the quality of mother-child interaction to prevent the adverse effects on the child? We propose to conduct a randomised controlled treatment trial of an intervention designed to improve the mother-child interaction as well as providing treatment for the mother's depression.

Second, can the putative parenting mechanisms whereby postnatal depression adversely affects child development be empirically tested? There is now considerable evidence for the operation of a number of mechanisms. However, this evidence has principally come from observational studies, including longitudinal ones (Field 1995 and Murray and Cooper 2003) and, as Rutter points out, this is not sufficient to impute causal relationships (Rutter 2005, 2007). The mechanisms have generally not been subjected to experimental examination, although a study by Field's group (Malphurs et al 1996) did indicate that manipulating specific maternal behaviours brought about improvements in responsiveness to the infant. A

treatment trial provides the opportunity for a quasi-experimental elucidation of the parenting mechanisms underlying the transmission of disturbance.

There is considerable evidence that both genetic and environmental factors play a role in child development (see reviews by Rutter et al 2006; Thapar and Rutter2008). This proposal focuses on environmental mechanisms because they are potentially modifiable by treatment. Thus the focus is on the parenting capacities that have been shown to be compromised in association with postnatal depression.

The impact of postnatal depression on maternal parenting capacities and mother-child interaction

Depression is characterised by low mood, withdrawal, hostility, irritability, and recurrent negative thoughts that are intrusive, difficult to dismiss and, when dismissed, recur. Research has shown that depression compromises the quality of the mother's caregiving, and suggests that disturbances in parenting are key mechanisms by which maternal depression affects child development (Murray and Cooper 2003). There are several related, partially overlapping, dimensions of parenting that have been identified as significant: notably, the missing of infant cues, lack of contingent responsiveness, intrusiveness, and poor facilitation, as well as low parental mood (Field 1995 and Murray and Cooper 2003). While lack of 'sensitivity' is often used as a generic term to cover these difficulties, sensitivity has often been defined and measured in rather different ways, and the measurement instruments used have also varied widely between studies. As de Wolff and van IJzendoorn 1997 point out, it is important to specify more precisely the ways in which particular parenting difficulties may affect different aspects of infant and child development, with a multi-dimensional approach to parenting antecedents of child difficulties replacing the broad focus on general sensitivity. Indeed, within the context of research into the effects of maternal depression, studies (including our own) have suggested that distinct aspects of maternal caregiving mediate the effects of the maternal disorder on several different infant and child outcomes, including cognitive development, behaviour problems and attachment (Milgrom et al 2004, NICHD Early Child Care Research Netowrk 1999, Campbell et al 2004, Murray et al 1193, 1996, 1999, Stanley et al 2004).

In order to advance the scientific understanding of the impact of depression on child development and to inform treatment, it is important to establish which aspects of parental functioning mediate the adverse effects of the disorder on child outcomes (see reviews by Rutter 2005 and by Scott 2008). There are three key maternal capacities that are likely to be adversely affected by depression, and that in turn compromise the child's outcome. While it

is likely that there is some generic effect of these capacities on outcome, there is also evidence that specific mediational processes may operate. The three capacities likely to be impaired by depression are:-

i) maternal focus of attention to child signals, and associated contingent responsiveness which, if impaired, compromises the development of the child's attentional capacities and cognitive ability.

ii) maternal emotional scaffolding, principally through warmth, consistent support and low levels of intrusiveness and coercion during stressful situations which, if impaired, adversely affects child emotional regulation and behaviour.

iii) the ability to treat the child as a psychological agent, as well as to provide (behavioural) sensitive responsiveness to the child's attachment-relevant needs, which, if impaired, increases the risk for insecure attachment.

We now discuss each of these three potential mechanisms in turn.

Maternal focus of attention onto infant behaviour and associated contingent responsiveness

A critical feature of depression is the cognitive process known as rumination (Nolen-Hoeksema 2000, 1991). This comprises recurrent negative thoughts that are intrusive and difficult to dismiss. Such thoughts absorb attention, leaving less available for the external environment (Gotlib and Cane 1987, Kahneman 1973, Posner and Rothbart 1980, McCabe and Gotlib and Cane 1987), including the infant (see Stein et al 2009 for review). This is important because focused maternal attention to the infant, and associated responsiveness that occurs contingently on infant cues and behaviour, is essential to the development of early learning (Yarrow et al 1987, Ruddy and Bornstein 1982). Thus, the mother's contingent responses to the infant teach the infant about connections between stimuli and responses, and help establish and develop the infant's own attentional skills (Stanley et al 2004, Papousek and Papousek 1997).

Several studies have demonstrated the negative effects of maternal depression or dysphoria on the mother's focus of attention and her support of her infant's attentional processes (Breznitz and Friedman 1988, Jameson et al 1997, Goldsmith and Rogoff 1997). For example, Kaplan et al 1999 found that where mothers had significant symptoms of depression in the postnatal period, their child-directed speech segments failed to promote associative learning in their 4 month-old infants. Our current Wellcome funded work has shown that mothers with postnatal depression are less likely to follow their infant's attention than controls, and their infants are more likely to ignore their mother's communication. Furthermore, we have found postnatal depression to have an adverse effect on infant

attention at 2 years, which is exacerbated if the depression becomes chronic. Finally, evidence from two of our earlier studies suggests that the focus of maternal attention and the associated contingent responsivity affects infant cognitive development (Murray et al 1993, 1996) and learning (Stanley et al 2004). Notably, the infant's ability to sustain attention and thus process information effectively, is one of the most robust predictors of IQ in later childhood (Slater 1995). In sum, it seems likely that a major cause of the association between PND and adverse child cognitive development is the compromised maternal focus of attention on the child and associated lack of contingent responsiveness, leading to impairment in the development of infant attention and cognitive functioning.

Emotional scaffolding

There is increasing evidence for parental influences on infant and child emotional and behavioural development. For example, parental warmth predicts low levels of externalising behaviour (Caspi et al 2004 and Eisenberg and Spinrad 2004), whereas negative, inconsistent and coercive parenting predicts high levels of such problems (Patterson 1982, Capmpbell 1995). Central to this process is the parent's promotion of child emotional regulation; this concerns the monitoring, evaluating and modifying of emotional reactions to both internal and external stimuli, so as to achieve a well-regulated state (Thompson 1994). The development of the capacity for emotion-regulation begins very early (Sameroff and Emde 1989, Jahromi et al 2004), and plays an important role in subsequent child adjustment (Kochanska et al 1998, 2003, DeGangi et al 2000). Accumulating research suggests that a certain kind of parental support (particularly in times of infant distress) which can be termed 'emotional scaffolding', plays a key role in promoting infant emotional regulation (Stern 1985, Kogan and Carter 1996, Carter et al 1990, Weinberg et al 1999, Braungart-Rieker et al 1998, Haley and Stansbury 2003). Broadly, this refers to the parent providing support for the infant, especially when distressed, so that the infant recovers his/her emotional equilibrium. As the infant matures, parental support for the infant's *own* developing capacities for self-regulation becomes increasingly important, (see Tronick and Gianino 1986, Tronick 1989, Weinberg et al 2006). Such parental behaviours both modulate concurrent infant negative affect, and support the development of subsequent self-regulated behaviour (e.g., Feldman et al 1999, Crockenberg et al 2008).

Failure to provide such emotional scaffolding appears to be a key aspect of parenting difficulty occurring in the context of depressive disorder. Depressed mothers tend either to withdraw from their infants, thereby failing to notice infant cues and lend support if the infant is distressed, or they may act in an intrusive, hostile manner that disrupts and dysregulates

the infant's behaviour and physiological state (Malphurs et al 1996, Field et al 1990, Jones et al 1997). Similarly, Tronick and colleagues have shown how depressed mothers have difficulty in providing appropriate support for the infant's recovery from distress especially when the interactions are under strain (Weinberg et al 2006, Tronick and Weinberg 1997). There is now accumulating evidence that poor emotional scaffolding is a mechanism whereby maternal postnatal depression increases the risk of disturbances in emotional regulation and subsequent behavioural problems in the child. For example, in our prospective longitudinal study of the development of infants of postnatally depressed mothers, we found episodes of infant behaviour dysregulation to be immediately preceded by the mother's negating the infant's experience, often through intrusive or hostile interventions (Murray et al 1996). In turn, such maternal hostility predicted negative child self-cognitions at 5 years (Murray et al 2001), and emotional dysregulation, conduct problems and ADHD at 5 and 8 years (Morrell and Murray 2003). A similar pattern of associations was reported by Maughan et al 2007. These findings are consistent with research on older children showing that disruptive behaviour is associated with parental hostility and coercive control (see Hill 2002 for a review).

Behavioural sensitivity to attachment cues and the capacity to treat the child as a psychological agent

A range of evidence shows that certain aspects of parenting are associated with secure child attachment (see Belsky and Fearon 2008, and de Wolff and van IJzendoorn 1997) for reviews).

(i) Maternal behavioural sensitivity, generally defined as parental availability and appropriate responsiveness to the infant, has been shown in meta-analyses to be an important predictor of attachment security (de Wolff and van IJzendoorn 1997). While sensitivity has been operationalised in widely divergent ways, a meta-analysis of treatment studies indicates that when maternal sensitivity is defined specifically in terms of infant attachment cues it is a stronger predictor of attachment security than sensitivity defined more widely (Bakermans-Kranenburg et al 2003). These findings notwithstanding, there is also considerable evidence that a significant proportion of the variance predicting attachment security is *not* accounted for by behavioural sensitivity. In particular, sensitivity has been shown to only partially mediate the impact of parental attachment on child attachment, and this has been termed the 'transmission gap' (Slade et al 1999, van Ijzendoorn et al 1995).

(ii) More recently, it has emerged that the parent's capacity to treat his/her child as a psychological agent is also a key aspect of parental functioning in relation to attachment. Two broad lines of work in relation to this capacity are especially relevant (Sharp and Fonagy

2008). The first concerns 'reflective functioning' which refers to parents' representations of children's thoughts and feelings; and particularly attachment-relevant aspects of relationships as described by Fonagy and colleagues 1991, 1997). The second concerns parental 'mind-mindedness', as developed by (Meins 1997, Meins et al 2003), which refers to more general parental representations during parent-child interactions. This entails the mother treating the infant as an intentional agent, and also includes her understanding that the child has representations of the world. The importance of reflective functioning and mind-mindedness has now been well demonstrated in relation to the child's attachment security (Meins et al 2001, Laranjo et al 2008, Grienenberger et al 2005).

Reflective functioning/mind minded parenting capacities are likely to be impaired in the context of maternal depression, since, in order to provide it, the mother would have to see beyond her own negative affective state, self-preoccupation and negative cognitions in order to monitor and reflect on the infant's experience. Indeed, there is evidence that mothers with high depressive symptoms have poorer reflective functioning than mothers with low depressive symptoms (Rosenblum et al 2008, Coyne et al 2007).

Thus, it would appear that there are two aspects of parental functioning are important in child attachment in the context of postnatal depression. The first is behavioural sensitivity to attachment cues (i.e. the capacity of the parent to support infant attachment behaviours); and the second is the capacity of the parent to understand their infant's experience and agency.

Treatment

Interventions

It has become clear that something needs to be done urgently to help mothers with postnatal depression in order to mitigate the negative effects on their children. There is good evidence that while it is now possible to successfully treat the mother's depression (Dennis 2009), treating the mother's depression alone does not significantly affect the mother-child interaction (Forman et al 2007, Nylen et al 2006, Poobalan et al 2007). Thus, in addition to providing treatment for depression, efforts need to be targeted directly at improving mother-child interaction in order to improve child outcome.

A limited number of treatment studies have been directed at interactions (Nylen et al 2006, Poobalan et al 2007). They have mostly shown some evidence of immediate improvement in

mother-child interaction but have generally been small-scale and have tended not to assess whether the effects are sustained. Two studies have reported positive effects of infant massage in facilitating mother-infant interactions in mothers with postnatal depression (Field 1997, Onozawa et al 2001). Field's group, in the context of a laboratory experiment, have targeted specific interaction styles in mothers with depression and demonstrated improved maternal interaction behaviours (Malphurs et al 1996).

With regard to child outcomes (in larger-scale studies), the results have been somewhat mixed. In relation to child behaviour, Murray et al 2003 evaluated the effect of non-directive supportive counselling, CBT and psychodynamic psychotherapy. They found that at 18-month follow-up, children of mothers in the therapy groups scored somewhat lower than the control group on behaviour problems, but there was no impact on cognitive development or attachment. Using more intensive toddler-parent psychotherapy, Cicchetti and colleagues found positive effects on both cognitive development and secure attachment, although the intervention only began when children were 20 months old and was delivered weekly for over a year (mean number of sessions = 45) (Cicchetti et al 1999, 2000). There have been two relevant intervention studies conducted in the developing world. In the first, conducted in Pakistan and beginning in pregnancy, a form of cognitive behaviour therapy was used and help was given to mothers with their infants (Rahman et al 2008). The rate of postnatal depression was reduced but there was no impact on child growth, the principal outcome. Parents reported that they played more with their children, although the quality of parent-child interaction was not measured. The second study was conducted by the applicants (Cooper et al 2009) in a deprived South African community, although not specifically in the context of depression. The home-based intervention focussed specifically on helping mothers to attend to the details of the infant's communication and to respond sensitively. It led to improvements in the quality of mother-child interaction and increased rates of secure attachment. It is thus becoming increasingly clear that treatments that provide direct access to the details of the mother-infant interaction are required to improve interactions and the child's outcome.

Video feedback intervention

One therapeutic technique showing considerable potential in addressing disturbances in mother-child interaction is video feedback. The most evaluated approach is that of Juffer, van IJzendoorn and Bakermans-Kranenberg 2008. The programme has been successfully used in a range of samples to enhance sensitive mother-infant interactions and improve child outcome for example: with adoptive children (Juffer et al 1997), chronically ill or preterm

children (Cassibba et al 2008), and temperamentally reactive infants (Klein Velderman et al 2006).

With support from the Wellcome Trust, we have successfully used video feedback techniques for mothers with eating disorders in the postnatal period. The mothers in this treatment trial also had high levels of depressive symptomatology (Stein et al 2006). This treatment was successful in enhancing the mother's responses to her infant's signals and initiatives, improving her facilitation of the infant, and it resulted in a marked decrease in mother-infant conflict and greater infant autonomy.

Recently a Dutch study, working with a postnatally depressed sample, used a number of therapeutic strategies including a general form of video feedback (van Doesum et al 2008). The treatment led to significant improvements in both child attachment security and child competence (cognitive outcomes were not measured). This study utilised a limited control group (3 x 15 minutes telephone support) (van Doesum et al 2008).

Treatment using video feedback is particularly promising for PND because it can address the three key hypothesised mechanisms involved in the transmission of disturbance. First, it can be used to focus on the core maternal attentional deficits that are hypothesised to lead to adverse cognitive outcomes. It does this by drawing the mother's attention towards the infant and away from her recurrent negative thoughts when the videotapes are revisited. The mother's attention is drawn to specific aspects of her infant's communication, attention and nuances of behaviour, and to instances of mother-infant mutual responsiveness. Second, video-feedback can enhance emotional scaffolding in three ways: (a) by providing emotional support for the mother; (b) by specifically identifying and reinforcing positive affective responses on the part of the mother; and (c) by reducing coerciveness and intrusiveness, using the 'wait, watch and wonder' technique (Cohen et al 2003). This will be done in our proposed trial mainly in the context of stressful situations as these are especially likely to elicit the relevant parenting behaviours. Third, video feedback can enhance the mother's capacity to treat the child as a psychological agent by using a number of specific techniques to help the mother consider the infant's perspective. For this, a range of different care-giving situations are observed, including those that focus on attachment issues. The therapist works with the mother to think about the meaning of the child's communication and offers different perspectives, not in a didactic form, but by wondering with the mother about the infant's communication and by using the 'speaking for the baby' technique (Carter et al 1991) which helps to verbalise possible interpretations of the infant's communication. Furthermore,

the therapist can help the mother identify the child's exploratory behaviour and attachment cues and to respond to them appropriately.

Utility of a primary care based intervention.

There is considerable evidence that treatments targeted at postnatally depressed women, especially the more vulnerable ones, need to be home based. This is because the combination of having a young infant and being depressed means that it is unlikely a mother will attend a clinic for therapy (Seeley et al 1996). It has recently been demonstrated that health visitors can identify and successfully treat postnatal depression in a home setting using cognitive behaviour therapy (CBT) or a person-centred approach (Morrell et al 2009). VFT has been developed for home-based treatment, so an intervention utilising both VFT and CBT is well-suited for home delivery. We have successfully piloted such an intervention in a sample of mothers with postnatal depression persisting to 6 months, providing therapy between 6-12 months. We have previously successfully utilised VFT and guided self-help CBT in our trial of mothers with postnatal eating disorders (Stein et al 2006).

5. OBJECTIVES

5.1 Primary Objective

In the context of postnatal depression, compared to a control treatment (PMR) does the index treatment (VFT) lead to better cognitive, behavioural and attachment outcomes in the children (where mothers in both groups receive CBT for their depression)? It is hypothesised that, compared to the control treatment, VFT will lead to better cognitive development, fewer behaviour problems, and a higher rate of secure attachment.

5.2 Secondary Objectives

Does video feedback operate by improving the quality of the three key parenting capacities discussed above? We will test the hypotheses that compared to the control treatment a)VFT will lead to greater improvements in the three parenting capacities (maternal attention on the infant and associated contingency; emotional scaffolding; and treating the child as a psychological agent and behavioural sensitivity to attachment cues); b) improvements in these capacities will mediate the effects of treatment on outcome; and c) each parenting capacity will be specifically linked to a particular conceptually related child outcome as follows:

- Improved maternal focus of attention on the infant and associated contingency will mediate better cognitive development

- Improved emotional scaffolding will mediate better emotional regulation and fewer behaviour problems
- Improved ability to treat the child as a psychological agent and behavioural sensitivity to attachment cues will mediate higher rates of secure attachment in the children

6. STUDY DESIGN

6.1 Summary of Study Design

The study is a randomised controlled trial. All participants will receive CBT. Participants will be randomised to a treatment arm, either VFT or PMR. There will be four minimisation criteria for the randomisation: child gender, socioeconomic status, infant negative emotionality, and severity of PND.

Those taking part will receive a baseline assessment, a home visit at which they will be given the opportunity to ask any questions and discuss the study, give informed consent, have baseline measures of them and their infants taken, and be randomised to a treatment arm. They will then receive twelve therapy sessions, all conducted in the home. The first five will be weekly, the next five will be fortnightly, and then the final two will be at 6 and 10 months after the end of the main ten therapy sessions (these latter two will be booster sessions). In addition, assessments will be conducted prior to the start of therapy, at end of the therapy (child age approximately 12 months), and again when the child reaches 24 month in age (approximately one year after the main therapy ends). Participants will receive a total of thirteen therapy and four assessment visits over a period of approximately 18 months. Visits may be divided further according to the convenience of the participants.

	Months postpartum						
	5-6	6-7	8-11	12	16	20	24
Recruitment							
Screening Interview							
Assessment I							
Weekly Therapy Sessions (5)							
Fortnightly Therapy Sessions (6)							
Assessment II							
Booster Therapy Session I							
Booster Therapy Session II							
Assessment III (2)							

6.2 Primary and Secondary Endpoints/Outcome Measures

Principal outcome variables at 24 months

1. *Child cognitive development* will be measured using the Bayley Scales of Infant Development-Third Edition (BSID-III). We will use the cognitive and language scales as the principal outcome. This is a widely used and validated measure of cognitive functioning at this age and has recently been updated.

2. *Behaviour problems* will be assessed by the Child Behaviour Checklist (CBCL) (2-3 year-old version) which is widely-used and well-validated. The principal outcome will be the externalising scale of the CBCL.

3. *Attachment security* will be measured by the Attachment Q-Sort (AQS), a 90 item q-set designed to measure the security of a child's attachment behaviour during naturalistic observations in the family home. It has been shown to be reliable with good discriminant validity. The items consist of numerous descriptors of behaviour typical of children between the ages of 12 and 48 months and these items are sorted by trained observers on the basis of extensive observations lasting for at least 1.5 hours.

Secondary outcome variables at 24 months

i) *Emotion-regulation*

Two standardised tests of infant temperament will be used to elicit emotion-regulation in the infants, taken from the LAB-TAB battery, the barrier paradigm and the restraint paradigm. Both are designed to examine emotional regulation in the face of potential frustration and anger. The mean of the emotional regulation scores will be used as a composite measure.

ii) *Attention*

- *Sustained Infant Attention*

  This will be measured using both manual responses by the child and eye-tracking using a version of the continuous performance test designed for use with 24-month-olds Early Childhood Vigilance Task.

- The Spatial Conflict Task (Geradi-Caulton, 2000.)

  This task has been validated with 24 month old children, and has been used in the literature. It takes approximately 5- 8 minutes to complete. It measures the relative benefit of a target being presented in a spatially congruent position to the response item, despite spatial information being irrelevant to task demands.

Summary: A touchscreen presents children with a response image (cat or dog) surrounded by a black rectangular border, in both of the bottom corners of the screen. For each trial, children are presented with a 'response image' in both of the bottom corners of the touchscreen, surrounded by a black rectangular border. A 'target' animal (cat or dog) is presented at one of various locations on the screen, and the child is instructed to touch 'response image' matching the 'target'.

Practice: 10 practice trials, without time-limit for response, allowing the experimenter to give verbal instructions and demonstrations to ensure that the child has understood instructions.

Test: targets are presented in a central location for 16 trials, and in lateral positions for 24 trials (with the target either on the same side of screen as the response image (congruent), or the opposite side of the screen (incongruent). 12 of each of the congruent and incongruent trials are run, in random order. For each trial, the target is presented for 3 sec, or terminated sooner if the child responds. Correct responses are followed by a 600 millisecond cartoon animation, but an incorrect, or no, response is followed by a blank screen for 600 milliseconds.

- The Visual Search Task (Gerhardstein & Rovee-Collier,2002)

  This task has been validated with 24 month old children, and has been used in the literature. It takes approximately 5- 8 minutes to complete. It measures the ability to select relevant stimuli (targets) while ignoring irrelevant distractors (non-targets).

  Summary: A touchscreen presents children with 90 stimuli, of which 20 are targets (animals), and 70 are distractors (objects), arranged randomly on the screen. The child is instructed to touch the target stimuli.

  Apparatus: Stimuli are presented on a colour monitor, equipped with infra-red LED touch sensitive hardware. Child sits at a distance of 30 cm.

  Procedure: Children are instructed to touch animals. A successful touch on a target results in the appearance of a star, which remains on screen for the remainder of the task, whereas a touch on a distractor results in no feedback. There is no time limit. The task ends automatically after 18 correct responses or 40 responses overall.

- Leiter International Performance Scale-Revised (Roid & Miller, 1997)

  This is a standardised assessment of non-verbal intelligence, fluid reasoning, visuospatial memory and attention for individuals aged 2 – 20 years, designed to be administered entirely non-verbally. The Leiter-R has two groupings of subtests:

'Visualization and Reasoning', and 'Attention and Memory'. The subtest for use in this study is 'Attention Sustained', which is part of the 'Attention and Memory' group.

The 'Attention Sustained' subscale is described to the child as 'The Drawing Game'. It consists of "boring" clerical tasks such as finding and crossing out all faces with smiles found in an array of images printed on a page. Three parallel forms, of increasing difficulty, are included, with a preschool "smiling face" form, an animal pictures form, and a more complex array of geometric shapes. In total, administration of the 'Attention Sustained' subscale typically takes between 4 and 6 minutes with a 2 year old child (depending on how much time is spent in the 'teaching' phase).

The subtest is administered with the child and researcher sat together at a table. A booklet is presented to the child, which contains test pages and teaching pages. Up to 2 minutes can be given to teach the child how to complete the task before beginning the first test page, and then another 30 seconds for each subsequent test page. Teaching is done by pointing back and forth between the 'response' picture at the top of the teaching page and one or more of the appropriate matching 'target' pictures. If necessary, the researcher can demonstrate crossing out one or more pictures, or gently place their hand over the child's and help them gently to cross out the appropriate 'target' pictures.

The booklet with arrays of faces, animals or geometric shapes is placed in front of the child with one side of images visible. Using gestures and nonverbal cues, it is indicated to the child that they should cross out as many of the 'target' pictures as possible that look like the 'response' picture at the top of the page during the allotted time. For each page, if necessary, up to two teaching cues can be given to the child.

There are a total of 4 test pages, with a maximum allocation of 30 seconds per page for the child to cross out the target images. Page 1 has 7 target items, page 2 has 10, page 3 has 23 and page 4 has 24. In most cases, the child will not find all the correct answers in the allocated time.

The child's raw score is calculated by 1) counting the total number of marks on the page; 2) counting the total number of correct marks per page, 3) subtracting the correct number form the total number of marks to obtain the total number of errors, 4) subtracting the total number of errors from the total number correct to obtain the raw score.

The raw score from the subtest is converted into a normalized score (M=10, SD = 3).

- Early Childhood Behavior Questionnaire (ECBQ). The ECBQ is a parent report measure of temperament in their 18 – 36 month old offspring. It has 3 factors

('Negative Affectivity', 'Surgency-Extraversion' and 'Effortful Control'), derived from 18 subscales, comprising 201 items.

The 'Effortful Control' factor comprises 8 subscales. Of these, three ('Attentional Focusing', 'Attentional Shifting' and 'Inhibitory Control') are proposed for measuring attention of 2 year olds in the OPT study. Each of these subscales comprises 12 items. 'Attentional Focusing' measures the sustained duration of orienting on an object of attention and resisting distraction. 'Attentional Shifting' measures the ability to transfer attentional focus from one activity / task to another. 'Inhibitory Control' measures the capacity to stop, moderate or refrain from behaviour under instruction.

- Emotional Discrimination Task
  Positive (happy), negative (sad) and neutral (calm) adult faces will be presented for 100 milliseconds each on a screen linked to an eyetracker to the children at 24 months. Attention-getters (cartoon images/movies) will be used in between each face of each battery of 12 face images as required to keep the child interested and attending to what is on the screen. Faces from the NimStim database will be used.

iii) *Maternal depression* will be measured at each time point using the EPDS and SCID. Depression at 24 months will be used as a secondary outcome. Although not an outcome variable, the fathers' depressive symptomatology will also be measured using the EPDS at each timepoint.

iv) Musical training and habits of the mothers will be measured at the final assessment via maternal report.

6.3 Study Participants

6.3.1 Overall Description of Study Participants

Mothers aged ≥ 18 years with a diagnosis of persistent postnatal depression at 6 months postpartum.

6.3.2 Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Aged 18 years or above.
- Mother 4½ - 9 months postpartum at screening (maternal mental state assessment).
- Mother has current PND which has lasted for 3 months or has current PND and evidence of PND in the postnatal 3 months.

- Diagnosed with postnatal depression with a Clinical Severity Rating (CSR) of ≥4.
- Infant born at ≥ 35 weeks gestation.
- Infant birthweight of ≥ 2000 grams.

6.3.3 Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Other severe psychiatric diagnosis. Includes bipolar disorder, schizophrenia, significant substance and alcohol abuse.
- Life-threatening or other serious physical illness in the mother.
- Serious illness or medical complication in the infant.
- Infant in Child Protection Plan (child protection register).
- Mother unable to converse in English.
- Mother not cohabiting with the infant.

6.4 Study Procedures

6.4.1 Recruitment

Potential participants will be identified and initially approached by their healthcare provider. This would be primarily the GP or health visitor, but may be a psychologist or other healthcare professional, when they see a patient with persistent PND. Whether in the primary or secondary care setting, the methods of approach would be the same. Where possible, potential participants will be approached face to face. They will be told about the study, and given an information pack to take away with them. They shall be invited to consider taking part, and discuss participation, perhaps with their partner, friend or family member. As part of the information pack, they would be given the means by which to contact the research team directly should they be interested in finding out more about it and possibly participating (telephone, email, freepost return envelope).

In addition, we will ask participating GP Practices to conduct searches of their databases to identify women that are potentially eligible for the study. The women would then be sent a letter from the Practice introducing the research study, along our information pack, screening questionnaire (EPDS) and methods by which to respond enclosed. Questionnaires and response methods will be made available online. Mothers who reach the EPDS cut-off of 13 or more will be contacted initially by telephone to assess further eligibility criteria before being invited to take part in the full assessment visit.

The main recruitment stream will be via the primary healthcare providers (GPs and health visitors). We also intend to utilise IPPS (Infant-Parent Perinatal Service) a specialist multi-professional service provided by the Oxfordshire and Buckinghamshire Mental Health NHS Foundation Trust (OBMH). Any of the healthcare staff within IPPS may approach potential participants (most likely they would be a psychologist).

Finally, we will be including information about the study on local parenting and mental health websites (such as www.mumsnet.com and www.netmums.com). These websites allow for the information to be included by locality and region and hence will only be included in the areas that we already recruiting. The information included will replicate the information in our poster.

6.4.2 Informed Consent

Full informed consent will be obtained at the first screening visit, prior to any assessment being undertaken. The assessor will ensure the participant has received all written information and will go through it to ensure it has all be understood. They will invite the participant to ask any questions they may have, and make it clear that they can ask questions as they come up throughout their participation in the study, and are free to withdraw at any time. Informed consent will be obtained in accordance with the OCTUMI SOP on Procedures for Obtaining Informed Consent.

6.4.3 Study Assessments

The research assessors will not be involved in any way with the treatment and will be blind to treatment condition. There will be three primary assessment points: (i) before treatment when the infant is 4½ - 9 months, (ii) at the end of the treatment when the infant is 12 months, and (iii) at follow-up a year later when infant is 24 months. At all three time-points assessments will be made in the family home. Interactions between mother and infant, using toys that we will provide, will be filmed and coded (by coders blind to therapy arm). At 6 months, a full assessment (using the SCID) of the mother's mental state will also take place. At the second assessment visit (child 12 months old) assessment of maternal appraisal of infant facial and vocal expression task, assessment of child attachment tasks ((i)mother/child play, audio clips to child in mother's absence, reunion (ii) assessment of the mother's manner in which she conveys information about different attachment scenarios to her child) will be conducted. In addition the CBCL and language scale of the BSID-III, and the Health Care Utilisation Questionnaire will be conducted. At the third assessment visit (child 24

months) an additional assessment will take place in our research unit to assess the child's cognitive and language development (Bayley BSIDIII), attention (ECVT, Leiter, Spacial Conflict and Visual Search tasks) and emotional regulation (Rothbart Lab-TAB). In addition, the Attachment Q-Sort will be conducted and the Health Care Utilisation Questionnaire will be given to the participant. Mothers will also be asked to complete a questionnaire on their musical training and habits. Mothers who have already completed the final assessment will be sent a copy via post/email (according to their preferred method).

In addition the EPDS will be repeated during the 6th therapy session to monitor maternal mood. Finally, assessments of the partners of mothers in the study will be conducted by questionnaire, in agreement with the mother, and where the partner chooses to opt-in. EPDS and GHQ-12 will be administered at each assessment point to gauge the partner's mental state. A health history questionnaire will also be administered (Partner Additional Questions). The partner's mental state will be analysed as a covariate.

Following completion of final assessment and collection of outcome data a sub-sample of participants (n=20) will be invited to take part in a qualitative sub-study investigating participant experiences of treatment.

The project will consist of two home visits. The first session will be an unstructured interview with only one overarching question asked "Can you tell me about how you found the therapy you received from the beginning, through the different sessions to the end". This will be followed by a series of specific questions based on the issues raised by the participant. The second session will comprise of a semi-structured interview. It will be used flexibly to follow-up questions raised during the first interview which we need to explore in more detail. The visits will last between 1-2 hours. Participants will be reimbursed £20 for each visit. The interviews will be conducted by a graduate student with prior experience conducting qualitative interviews. The conversations will be audio-recorded with the consent of the participants and all procedures outlined regarding data storage and confidentiality already in place will be followed.

Participants will be identified by the Trial Coordinator.

Participants will be approached during their last assessment with the study and the researcher will ask the mother if this is something she would be interested in hearing more about or taking part. If participants have already completed the final assessments the researcher who saw them last will contact and ask if they would be interested in hearing more about this. Following this their details will be passed on to the interviewer who will call to explain more about the study and arrange a home visit if they are interested.

All SOPs currently in place will also be used for this qualitative project detailed in Section 8 of the Protocol v.10.0. Supervision and consultation will be available by a Consultant Psychiatrist (PI to the study) in the event that the participant is distressed following the interviews.

Part of this work will be used by the research assistant working on the project for her Master's dissertation for Birkbeck College, London.

6.5 Definition of End of Study

The end of study is the date of the last visit of the last participant. The funding period of the study runs to 31 August 2015 and coding and analysis will continue beyond the date of the last visit.

7. INTERVENTIONS

The three therapies which constitute the study interventions are outlined here. All participants will receive Cognitive Behaviour Therapy (CBT). They will also be randomised to receive either Progressive Muscle Relaxation (PMR) or Video Feedback Therapy (VFT). All therapies will be delivered to each participant by the same therapist, and within the same visits (i.e. CBT and VFT/PMR at every therapy session). There will be five weekly sessions to begin with between 6-8 months , followed by five fortnightly sessions around 8-12 months, and then by two booster sessions at 16 and 20 months. At the end of session 3 the participants will be asked the extent they believe the treatments they have been allocated will help them (Expectation Questionnaire).

Cognitive Behaviour Therapy (CBT)

The purpose of CBT is to acquire skills for managing negative thoughts and feelings. CBT for depression targets behaviours that contribute to loss of positive reinforcement from others or the environment, and cognitions that represent negative beliefs about the self, world and future.

The first stage of the therapy is aimed at lessening depression using behavioural techniques, such as daily activity schedules, pleasant event scheduling, and problem-solving. These behavioural techniques are intended to increase sources of positive reinforcement, and to replace avoidant behaviours with problem-solving behaviours. The second stage of treatment works at identifying and challenging negative automatic thoughts. Information from behavioural experimentation are used to develop and strengthen more balanced ways of thinking.

Video Feedback Treatment (VFT)

The aim of the video-feedback treatment is to improve the quality of mother-child interaction by enhancing the three core parenting skills described previously. At most visits the therapist videotapes the mother and infant at home during general interactions and specific tasks. At the following visits, the therapist and mother watch and discuss extracts selected by the therapist to highlight the infant's signals and to draw out and enhance the mother's observational skills. The baseline assessment videotape is used in the first VFT session.

In order to help the mother with the three parenting capacities, a number of situations and tasks have been selected which enable the therapist to work with the mother on each capacity, as follows:

- Maternal focus of attention and associated contingency using book sharing and joint cognitive tasks.
- Emotional scaffolding using difficult and frustrating toys slightly above child's developmental level.
- Ability to treat the infant as a psychological agent and behavioural sensitivity to attachment cues using brief separations and exploration opportunities.

Treatment progresses by initially concentrating on the infant's perspective, focusing on his/her signals (initiatives towards the mother, exploratory behaviour, interest, and distress). In subsequent sessions this is augmented by highlighting the mother's perspective: mother-infant initiatives, mutual responses, moments of shared emotion and the success of sensitive, prompt reactions to infant cues. In the last few sessions the mother is also helped to identify and address potential triggers to specific difficulties.

Progressive Muscle Relaxation (PMR)

The relaxation training is based on Bernstein and Borkovec's (Bernstein and Borkovec 1973) progressive muscle relaxation training and was developed to reduce tonic levels of arousal and anxiety and to be a tool for coping with stressful events. Participants are taught that cognitions and physical symptoms are connected and affect each other reciprocally, and therefore learning relaxation may lead to increased mental well-being. The programme consists of relaxation training involving progressive tensing and relaxing of 16 muscle groups, then 8, and finally just four muscle groups. Throughout, the participant is asked to concentrate on the sensations she experiences during tensing and relaxation. The next stage is relaxation-by-recall, where the participant is asked to think about what the relaxed state feels like, rather than actually tensing and relaxing muscles. The last stage of the

training consists of pairing the exhalation of a deep breath with the thought 'relax' (cue-controlled relaxation). CDs or audiotapes containing the relaxation procedure are given to the participant and she is asked to practise at home.

More detail on all three of these therapies can be found in the Therapy Manual accompanying this protocol.

At the beginning of each session the participant will be asked to complete the PHQ-2 (2 items) to assess their mood to allow us to monitor the progress of their mental state.

8. SAFETY

All research staff will be required to undergo Enhanced CRB checks.
It is not anticipated that any serious adverse events will occur. Safety will be kept under review by the Trial Steering Committee and Data Monintoring and Ethics Committee and any serious adverse event will be reported to the sponsor and the REC within 15 days.

8.1 Staff Safety

A risk assessment on home visits will be conducted prior to the study commencing and a specific plan of action put in place for recording the researcher's whereabouts (e.g telephoning on arrival at home visit and on departure). Further detail of this 'buddy system' can be found in SOP Risk & Safety: Home Visits.

8.2 Child Protection

If there are significant child protection concerns we will follow the OBMH protocol, Safeguarding Children, in the event of such issues arising. The therapists will always be in close contact with the CI.

8.3 Safeguarding Vulnerable Adults

Working with vulnerable adults, it is important to ensure they are safeguarded. We will follow the OBMH protocol, Safeguarding Vulnerable Adults. We will ensure it is made clear to healthcare professionals, participants and research staff that clinical responsibility lies with the healthcare professional whose care the participant falls under (usually the GP).

9. STATISTICS AND ANALYSIS

9.1 Number of Participants

The target number of participants is 144 (72 in each arm). The sample size calculation is based on the Bayley Mental Development (MDI) Index using the Bayley second edition. Cornish and colleagues (2008) report summaries of the Bayley MDI scale in 15-month-old children according to PND in mothers – no history, brief PND and chronic PND. Based on a standard deviation of 10.9, as reported for those children with mothers suffering chronic PND, a sample size of 57 per group is necessary to detect a difference of 5.8 (as found by Cornish) in the Bayley MDI scale, at the 5% significance level with 80% power. Allowing for 20% loss to follow-up, a conservative estimate given the low attrition in our trials to date (Stein et al 2006, Cooper et al 2003), 72 participants per group are required.
This study uses the Bayley Scales of Infant Development III to measure the main outcome. It gives a score for cognitive and language development. The previous version of this measure provided with an aggregate score of cognitive, language and fine motor development known as the Mental Development Index. The Third edition of this measure does not provide an aggregate score; the sub scales (cognitive and language development) are used separately.
Our original sample size calculation was based on published data using the Bayley (version II). With respect to the cognitive and language subscales available in the Bayley (version III), the proposed sample size will have 80% power to detect a difference of 0.532 standard deviations between the randomised groups.

Piteo and colleagues (2012) report Bayley III cognitive and language subscale scores at 18 months in 69 children of mothers with maternal depression in the first six months postpartum. The standard deviations for cognitive and language subscales were 11.9 and 13.5 respectively. Assuming similar levels of variability are seen in this trial, our proposed sample size of 57 per group will have 80% power to detect a minimum difference of 6.3 in the cognitive scale and 7.2 in the language scale of Bayley III.

9.2 Analysis

With regard to child behaviour problems, a sample size of 57 allows for differences between groups of 0.532 standard deviations to be detected at the 5% significance level and 80% power. Trapolini and colleagues (2007) report Child Behaviour CheckList (CBCL) maternal ratings of externalising behaviour in 4-year-olds. These were grouped according to mothers' depression, as never, sometimes and chronic. The standard deviation of the mothers' scores in the chronic depression group was 7.70, which would allow a difference of 4.08 to be detected if similar variability was observed in this trial. The means and standard deviations in our current Trust programme on the 65% of the sample analysed so far, for 2-year-old children of mothers who remain depressed at 6 months, are very similar to those of Trapolini.

For attachment, van Doesum and colleagues (2008) report Attachment Q-Sort (AQS) security in children 18 months of age, with a common standard deviation of 0.326, which would allow for a difference of 0.17 to be detected if similar variability was observed in this trial.

It is hypothesised that, compared to the control treatment, VFT will lead to better cognitive development, fewer behaviour problems, and a higher rate of secure attachment (Hypothesis 1). To test Hypothesis 1 ANOVAs will be conducted (with each of the child outcomes measured at 24 months as the dependent variable and the treatment group as a between-group factor). The three secondary outcome variables will be analysed similarly. Hypothesis 2 has three components: (i) to examine whether, compared to the control group, VFT leads to greater improvement in the three parenting capacities, ANCOVAs (co-varying for the 6m baseline measure) will be performed on each capacity; (ii) to test for mediation, initially the role of single mediators will be examined using standard regression analysis (including any relevant covariates) (Kraemer, et al, 2002); (iii) to establish the unique contribution of each mediator (since the potential mediators might be associated), exploratory mediational analysis using bootstrapping techniques will be conducted (in line with Preacher et al 2007), that include the two non-targetted maternal capacities as covariates. Given the increased complexity of the models including covariates, and our sample size, bootstrapping techniques will be used to also provide confidence intervals (after MacKinnon & Fairchild, 2009).

Qualitative Data on the experience of therapy

The qualitative data collected from the sub-study on the perception of treatment will be analysed using Interpretative Phenomenological Analysis by a researcher trained in qualitative research. The analysis is based on reading the transcript of each interview and involves a systematic search for themes as evidenced in the text. Themes are then examined across cases to examine where they converge and diverge resulting in the establishment of a table of superordinate themes.

Validating a subset of Bayley III items

Separate analysis will be conducted to rescore and examine a subset of Bayley III items and how they related to the complete Bayley III scales for cognitive and language development. This will be a sub study using data collected from the OPT study. For this age group administration of the measure for the cognitive and language scales takes between 45 - 90 minutes. This requires substantial time commitment on the participants' side. Researchers from the team and the department of Psychiatry who specialize in child development have

identified a subset of items that are representative of language and cognitive development in two year old infants.

We will test whether this subset of items provides a reliable index of child development in comparison to the full Bayley scales. This would be invaluable for researchers in low resource settings and where less time is available.

Currently the Bayley scales are scored as a Yes/No item (whether the child has or hasn't attained the item).
We will examine how scores on this subset correspond to the full Bayley scales for Cognitive and Language development. Second, we will use the already video-recorded Bayley assessments to score the items using a different scoring system consisting of four options (instead of Yes/No): item was passed in under 3 attempts, items passed in 4-5 attempts, item failed and item not attempted. We believe that this scoring will provide greater discrimination.

10. ETHICS

10.1 Participant Confidentiality

The study staff will ensure that the participants' anonymity is protected as far as possible. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

Personal addresses, telephone numbers etc. will be stored separately (in a locked filing cabinet, in a separate office) from research data (audiovisual footage and clinical data). Each participant will be given a subject number, and an electronic file linking the subject number to the participant will be stored on a University of Oxford networked drive, accessible only to members of the research team, in a password-protected file. Any clinical or coded data will be referenced only by a participant's subject number, not their name or other details.

Publication of direct quotations will always be anonymised, and specific consent sought for this use.

Audiovisual recordings are stored in a locked cabinet in a separate office from personal data, and are backed up on a secure University of Oxford network with very limited access (i.e. only to senior research team members and researchers working directly with a particular participant or directly involved in coding data). Specific additional consent will be requested

for use of audiovisual recordings in presentations, and it made clear to participants that anonymity could not be guaranteed in this event. Participants will be given the option to not have any audiovisual recordings used outside of the team of researchers and this is clearly outlined in the consent form.

10.2 Other Ethical Considerations

Infants

The infants participating in this study are obviously unable to consent or assent to their involvement (being aged 6-24 months). Their involvement is crucial in order to answer the research question as to whether the VFT treatment mitigates the adverse impact of the mother's PND on the infant and enhances infant development.

Vulnerable Group

Women with PND potentially constitute a vulnerable group. They are essential to this trial, as it is the impact of their disorder that is to be studied. The PIs and other research staff on the team have worked with women in the postnatal period for many years and are experienced and sensitive to their needs. A great deal of time and consideration is committed to explaining the study and giving the participants regularly opportunities to ask questions. Beyond the initial consent, it is reiterated that participants are not obliged to take part and free to withdraw at any time.

Provision of Therapy

A particular issue with this study is the provision of therapy. Women who may not otherwise by offered CBT, or who may have to wait for CBT or only be offered group therapy or computerised CBT at a less convenient location than her home, will be offered CBT as part of this study. CBT is a standard therapy offered by the NHS to those suffering from persistent depression. We realise that this may make the study appear more attractive, both to primary care staff and to potential participants. We will ensure the time commitment and research nature of the other therapies and assessments are made clear to all. We will not be able to continue provision of therapy beyond the duration of participation in the study. We will, however, liaise with healthcare professionals involved in a participant's on-going care, to ensure their current needs are recognised. It is not standard practice for a course of CBT to run to more than thirteen sessions (which is the number of sessions we are providing) within a primary care setting**.**

Exclusion Criteria

As far as we can we will be as inclusive as possible. The only criteria on which we would exclude potential participants are those that make the conduct of therapy impossible (not sufficient), where a potential participant has another severe psychiatric disorder requiring a different form of treatment, and where the infant has a serious developmental problem which would impact independently on the outcomes.

Confidentiality in an 'at risk' population

Whilst we would maintain the confidentiality of participants at all times, it may be necessary to break that confidentiality where there is a significant risk of harm to either the mother or the infant. This would only be done following clinical protocol in close consultation with Chief Investigator, who is a Consultant Psychiatrist.

Remuneration of Participants

Payments to participants will be made for the assessment visits only at a rate of £20 per visit. This will amount to £80-100 per participant over the 18 month period of participation. An additional payment of £20 for each visit will be made to participants taking part in the qualitative sub-study investigating the perception of treatment (n=20).

As this is a therapeutic trial, utilising an existing proven therapy (CBT) in all participants, we do not feel it to be appropriate to remunerate participants for the therapy sessions.

Post-Trial Provision of Treatment

While there is no specific arrangement for on-going provision of the therapies beyond the duration of participation in the study, if participants still require treatment we will (with the participant's permission) liaise with healthcare professionals involved in their care to facilitate this. We will liaise with the GP on an on-going basis throughout the study, and it's conclusion, where necessary. Ultimately, participants will be returned to normal care with information being supplied to healthcare professionals involved in their on-going care.

11. TRIAL STEERING COMMITTEE (TSC) & INDEPENDENT DATA MONITORING AND

ETHICS COMMITTEE (IDMEC)

The members of the Trial Steering committee (TSC) of the OPT Study are Prof Emily Simonoff (chair), Dr Mario Cortina Borja, Dr Penny Moore and Mrs Sarah Man. The first TSC meeting will take place before the first participant is randomised and will then meet annually.
The members of The Independent Data Monitoring and Ethics Committee (IDMEC) are Dr Ron Gray, Dr Jonathan Evans and Mr Ed Juszcak and will meet as required.
The trial statistician is Dr Ly-Mee Yu, Senior Medical Statistician (Centre for Statistics in Medicine, Oxford University).

12. DATA HANDLING AND RECORD KEEPING

In accordance with OCTUMI SOP on Trial Master Files all essential documents, enabling the conduct of the trial and the quality of the data produced to be evaluated, will be collated in a Trial Master File. In accordance with OCTUMI SOP on Data Management, all study data will be entered onto a suitable database. The participants will be identified by a study specific subject number and/or code in any database. Names or initials will NOT be included in any study data electronic file.
In accordance with OCTUMI SOP on Archiving of Essential Documents, audiovisual and other data will be retained for 3 years following the youngest participants' 18th birthday (approximately 25 years altogether). It will be stored on University of Oxford secure archiving facility, and in locked filing cabinets accessible only to authorised staff.
OpenClinica software will be used for the OPT study data capture and trial data management.

13. FINANCING AND INSURANCE

This study is funded by the Wellcome Trust as a Programme Grant, reference 090139, total award amount £1,478,756. Indemnity and/or compensation for negligent harm arising specifically from an accidental injury for which the University is legally liable as the Research Sponsor will be covered by the University of Oxford.

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15. APPENDIX A: STUDY FLOW CHART